Testosterone
The importance of Testosterone

Testosterone-deficient

- Dry, thin hair
- Pale face
- Dry eyes
- Small wrinkles
- Hypotonic face muscles
- Small wrinkles
- Poor beard & moustache

Testosterone-sufficient

- Wrinkles
- Dry eyes
- Pale face
- Small wrinkles
- Hypotonic face muscles
- Poor beard & moustache
Testosterone-deficient

Testosterone – excessive
TESTOSTERONE ENANTHATE 100 mg injections in aging men & effects on serum lipoproteins

**Figure**: effects of 3 month of 100 mg testosterone enanthate injections (1 x/week) or placebo injections in 13 healthy men aged 57-76 years old

*(Tenover JS, J Clin Endocrinol Metab, 1992, 75: 1092-1098)*
Testosterone

=> ↓ Serum Total cholesterol
TESTOSTERONE ENANTHATE 100 mg injections in aging men & effects on serum lipoproteins

Figure 1: Effects of 3 month of 100 mg testosterone enanthate injections (1 x/week) or placebo injections in 13 healthy men aged 57-76 years old (Tenover JS, J Clin Endocrinol Metab, 1992, 75: 1092-1098)
American Heart association

# Total Cholesterol

<table>
<thead>
<tr>
<th>Total Cholesterol Level</th>
<th>Category</th>
</tr>
</thead>
<tbody>
<tr>
<td>Less than 200 mg/dL</td>
<td>Desirable level that puts you at lower risk for heart disease. A cholesterol level of 200 mg/dL or higher raises your risk.</td>
</tr>
<tr>
<td>200–239 mg/dL</td>
<td>Borderline high</td>
</tr>
<tr>
<td>240 mg/dL and above</td>
<td>High blood cholesterol. A person with this level has more than twice the risk of heart disease as someone whose cholesterol is below 200 mg/dL.</td>
</tr>
</tbody>
</table>
Serum cholesterol

1 mmol/l = 39 mg/dl  (38,647 mg/dl)

3 mmol/l = 115 mg/dl
5 mmol/l = 193 mg/dl
8 mmol/l = 308 mg/dl
Men with ↓ serum cholesterol => ↑ life expectancy

Men with low serum cholesterol
(less than 200 mg/dl)

Increase in life span

+ 3.8 yrs

n = 92,488 men
(18-39 yrs)

+ 8.7 yrs

Figure: Data from 3 studies:
Chicago Heart Association project (n= 11,017 men (18-39 yrs) followed in 1967-1973;
Peoples Gas Company Study (n= 1266 men (25-39 yrs) followed in 1959-1963;

A constant, progressive, solid & independent exists between serum cholesterol & long term risk of coronary disease & cardiovascular mortality versus men with low cholesterol.

Testosterone

=> ↑ Serum HDL cholesterol
American Heart association

**HDL Cholesterol**

<table>
<thead>
<tr>
<th>HDL Cholesterol Level</th>
<th>Category</th>
</tr>
</thead>
<tbody>
<tr>
<td>Less than 40 mg/dL</td>
<td>A major risk factor for heart disease.</td>
</tr>
<tr>
<td>40–59 mg/dL</td>
<td>The higher your HDL level, the better.</td>
</tr>
<tr>
<td>60 mg/dL and above</td>
<td>An HDL of 60 mg/dL and above is considered protective against heart disease.</td>
</tr>
</tbody>
</table>
Figure: A high HDL cholesterol is a sign. protector against all-cause mortality, & near sign. protector against cardiovasc. dis. mortality.

n = 7175 Japanese residents ; 9.6 yrs of foloow-up
Okamura T, .....Ueshima H;The inverse relationship between serum high-density lipoprotein cholesterol level and all-cause mortality in a 9.6-year follow-up study in the Japanese general population. Atherosclerosis. 2006 Jan;184(1):143-50  JShiga Un.apan
LDL Cholesterol ↑ with age

HDL Cholesterol ↓ with age in men

Atherogenic ratio LDL/HDL Cholesterol ↑ with age
The blood HDL cholesterol level increases and the level of the VLDL cholesterol declines proportionately to the increase of testosterone in the blood.

247 men of middle age participated in this study. The extreme values of blood levels of testosterone were for the three groups respectively 780-5330, 6.420-7.610 and 9.370-16.500 pg/ml.

(Gutai J et al, AM J Cardiol, 1981, 48 : 897-902)
Plasma Testosterone $\Rightarrow$ Serum Lipids

- The higher $\uparrow$ the plasma testosterone:
  - The higher $\uparrow$ the HDL cholesterol (+ 12% for the highest quartile) (in 391 men aged 30-79 years) (1,2,3)
  - The $\downarrow$ the VLDL cholesterol (1, 3)
  - The $\downarrow$ the triglycerides (3)

The higher $\uparrow$ the plasma DHT:

- The higher $\uparrow$ the HDL cholesterol (4) (in coronary heart disease patients)

Oral testosterone undecanoate (Andriol®) in men with coronary heart disease:
- ↓ E$_2$/testo : ↓ testo, E$_2$ =
- ↓ sign. total cholesterol, ↓ TG, HDL =
- apolipoproteins A & B =


Injectable testosterone esters (Sustanon®)

in coronary heart patients (60-75 years):
- ↓ thromboxane A-2 => ↓ constrictory peptide
- ↑ prostaglandins 2 => ↑ dilatatory peptide

peptides that have dilatatory & constrictory effects on the coronary arteries
**HDL - CHOLESTEROL & TESTOSTERONE THERAPY**

**Figure**: Effect of various androgen medications during 12 weeks each on HDL-cholesterol in 18 young health men. No effect on total cholesterol, total triglycerides or insulin levels from these preparations. *(Friedl KE et al, 1990)*
Testosterone

=>

down Serum Triglycerides
Serum Testo => correlated negatively w/ Serum Triglycerides & Lipoprotein a

Figure: Low plasma T level may be a risk factor for coronary heart disease, which may relate to the changes of plasma lipoproteins.

Men + normal testosterone (> 270 ng/ml)

Men + low testosterone (< 270 ng/ml)

Serum levels (% versus healthy controls)

Triglycerides

Lipoprotein a

HDL cholesterol

n = 201 subjects, among them 102 patients + coronary heart disease & 99 healthy subjects

Zhao S, Li X, Wang Z. Plasma levels of lipids, lipoproteins and apolipoproteins affected by endogenous testosterone. Hunan Yi Ke Da Xue Xue Bao. 1998;23(3):299-301 Hunan Medical University, Changsha
American Heart association

**Triglycerides**

<table>
<thead>
<tr>
<th>Triglyceride Level</th>
<th>Category</th>
</tr>
</thead>
<tbody>
<tr>
<td>Less than 150 mg/dL</td>
<td>Normal</td>
</tr>
<tr>
<td>150–199 mg/dL</td>
<td>Borderline high</td>
</tr>
<tr>
<td>200–499 mg/dL</td>
<td>High</td>
</tr>
<tr>
<td>500 mg/dL and above</td>
<td>Very high</td>
</tr>
</tbody>
</table>
Men with ↑ serum triglycerides

=> ↑ risk of ischemic heart disease

Serum Triglycerides

<table>
<thead>
<tr>
<th>tertile</th>
<th>Lowest tertile</th>
<th>Middle tertile</th>
<th>Highest tertile</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ischemic heart disease</td>
<td>1.0 (1.0-2.3)</td>
<td>1.5 (1.0-2.3)</td>
<td>2.2 (1.4 - 3.4)</td>
</tr>
<tr>
<td>(Relative risk)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n = 2906 white men</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Figure: Men belonging to the highest tertile of serum triglycerides have an increased risk of developing ischemic heart disease (8 yrs of follow-up, initially aged: 53 - 74 yrs, 229 on 2906 developed the disease).

Testosterone =>

↓ Lipoprotein a
Lipoprotein a

Serum lipoproteine a => should be

< 24 mg/dl (Cheng 2001)

or < 30 mg/dl (Koda 1999)


Koda Y, Nishi S, Suzuki M, Hirasawa Y. Lipoprotein(a) is a predictor for cardiovascular mortality of hemodialysis patients. Kidney Int Suppl. 1999 Jul;71:S251-3. Kidney Center of Shinraku-en Hospital, Niigata University, School of Medicine, Japan. WG8Y-KUD@asahi-net.or.jp
Men, not women, with ↑ lipoprotein a
=> ↑ mortality

Relative Risk
(adjsuted for age, sex,; other risk factors such as total & HDL cholest., triglycerides; carotid-wall thickness; smoking or little effect)g status; diabetes or not,& systolic & diastolic hypertension had no or little effect)

n =5888 community-dwelling older adults (65 years of age or older) in the United States,2375 women and 1597 men

Figure: Similar analyses for women, which also included adjustment for estrogen use or nonuse, revealed no such relation.

Lipoprotein a  - Lp(a) – part 1

• **What is Lp-a?** = a lipoprotein particle found in the bloodstream. The structure of the Lp-a particle is very similar to an LDL particle linked to a plasminogen molecule. Plasminogen is involved in dissolving blood clots. The function of Lp(a) is unknown.

• **How is Lp-a related to atherosclerosis?**
  Lp-a is a marker for the development of atherosclerotic vascular disease. Individuals with elevated Lp-a are definitely at an elevated risk of developing atherosclerosis. Whether Lp-a is directly involved in the atherogenic process has not been determined. The concentration of Lp-a is race specific.

• **How is Lp-a treated?** Treatments of Lp-a are very few. Nicotinic acid (vit. B3) has been shown to lower concentration of Lp-a to a small degree as well as estrogen supplementation.

*Preventive Cardiology website - Victoria*
Serum Testo => correlated negatively w/ Serum Triglycerides & Lipoprotein a

Men + low testosterone (< 270 ng/ml)

Triglycerides

1.47 vs 1.10 mmol/L

+ 34 %

Lipoprotein a

25 vs 17 g/L

+ 47 %

HDL-cholesterol

1.31 vs 1.44 mmol/L

-11 %

0.88 vs 1.02 mmol/L

-14 %

p < 0.05 for all

Figure: Low plasma T level may be a risk factor for coronary heart disease, which may relate to the changes of plasma lipoproteins.

n = 201 subjects, among them 102 patients + coronary heart disease & 99 healthy subjects

Zhao S, Li X, Wang Z. Plasma levels of lipids, lipoproteins and apolipoproteins affected by endogenous testosterone. Hunan Yi Ke Da Xue Xue Bao. 1998;23(3):299-301 Hunan Medical University, Changsha
<table>
<thead>
<tr>
<th>Serum testosterone: Lipoprotein a</th>
<th>Patients-Controls</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>an inverse correlation between T &amp; Lp(a) ( (r=-0.24, P=0.04) )</td>
<td>108 postmenop. women (age 62+/-7 yrs)</td>
<td>Kaczmarek A, Int J Cardiol. 2003 Jan;87(1):53-7</td>
</tr>
<tr>
<td>a negative assoc. between serum Total testo &amp; serum TG level &amp; Lp-a ( (r=-0.163,P&lt;0.05) )</td>
<td>201 subjects, among them 102 patients with CHD and 99 healthy subjects</td>
<td>Int J Cardiol. 1998 Jan 31;63(2):161-4</td>
</tr>
<tr>
<td>No difference in homocysteine</td>
<td>47 p. (5 men; 38 yrs) + SH &amp; 50 controls (4 men; 34 yrs)</td>
<td>Aldasouqi S, Endocr Pract. 2004 Sep-Oct;10(5):399-403, Saudi Arabia</td>
</tr>
</tbody>
</table>
Chemical castration => reduced or increases Lp-a!

<table>
<thead>
<tr>
<th>Serum testosterone</th>
<th>Patients-Controls</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>GnRH analog triptorelin =&gt; sign. increased serum Lp-a from 278 to 377U/l (P=0.004)</td>
<td>10 healthy men + serum testo reversibly suppressed for 5 weeks</td>
<td>Kaczmarek A, Int J Cardiol. 2003 Jan;87(1):53-7</td>
</tr>
<tr>
<td>Suppression of testosterone =&gt; sign. increased serum Lp-a from 5.5 to 8.5 mg/dL</td>
<td>12 healthy young men + during 3 weeks daily s.c. inj. of Cetrorelix, a GnRH antagonist</td>
<td>von Eckardstein A, J Clin Endocrinol Metab. 1997 Oct;82(10):3367-72</td>
</tr>
</tbody>
</table>
### Serum testosterone => no assoc. w/ Lp-a

<table>
<thead>
<tr>
<th>Serum testosterone: Lipoprotein a</th>
<th>Patients-Controls</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>No correlation w/ Lp-a, nor CRP</td>
<td>715 healthy middle-aged men</td>
<td>Van Pottelbergh I, Atherosclerosis. 2003;166(1):95-102</td>
</tr>
<tr>
<td>No changes in Lp-a in the study population as a whole, but a 17.6% (p &lt; 0.05) reduction in the subjects + high pre-treatment Lp(a) (&gt; 20 mg/dL).</td>
<td>62 healthy obese patients (21 men aged 32 +/- 9.6 years and 41 women aged 37 +/- 14.6 years</td>
<td>Nutr Metab Cardiovasc Dis. 2001 Jun;11(3):153-7</td>
</tr>
<tr>
<td>Lp(a) concentrations were not related to all hormonal &amp; clinical parameters ; Lp(a), did not change sign. after treatment</td>
<td>22 + idiopathic hypogonadotropic hypogonadism &amp; 9 + Klinefelter's syndrome</td>
<td>Ozata M, J Clin Endocrinol Metab. 1996 Sep;81(9):3372-8</td>
</tr>
<tr>
<td>Lipoprotein(a) levels increased by similar amounts in both (testosterone treated, 3 mg/dL; placebo treated, 4 mg/dL; P = 1.0).</td>
<td>108 healthy men &gt; 65 years + serum testons &gt;1 SD below the mean for young men</td>
<td>Snyder PJ, Am J Med. 2001 Sep;111(4):255-60.</td>
</tr>
</tbody>
</table>
Testosterone reduces Lipoprotein a

Figure: testosterone reduces Lp(a) in men primarily by an anabolic effect and not by its conversion to estradiol. Publication


<table>
<thead>
<tr>
<th>Testosterone =&gt; lipoprotein A</th>
<th>N = participants</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Short 16 wks transd. testo =&gt; no change of Lp-a, nor CRP</strong></td>
<td>Postmenop. women + transd. estrogen for at least 8 weeks + 2 mg/d of transd. testo</td>
<td>Davies SR, Menopause. 2006;13(1):37-45 Australia</td>
</tr>
<tr>
<td><strong>Non sign. reduction of Lp-a with testosterone.</strong></td>
<td>50 women + surgical menopause + oral 2 mg of E2 valerate + 40 mg of Testo undecanoate or placebo for 24 wks</td>
<td>Floter A, Maturitas. 2004 20;47(2):123-9 Sweden</td>
</tr>
<tr>
<td><strong>Lo dose testo =&gt; no differences in Lp-a</strong></td>
<td>22 women + severe PMS (39.6 yrs) + subcut. T implants (100 mg/6 months) for at least 2 yrs</td>
<td>Buckler HM, Clin Endocrinol (Oxf). 1998 Aug;49(2):173-8</td>
</tr>
<tr>
<td><strong>Testo =&gt; no effect on Serum Lp(a)</strong></td>
<td>22 + idiopathic hypogonadotrophic hypogonadism &amp; 9 + Klinefelter's syndrome</td>
<td>Ozata M, J Clin Endocrinol Metab. 1996 Sep;81(9):3372-8</td>
</tr>
</tbody>
</table>
The End